PROJECT

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1) Project title
Metabolic Adaptations in Chemoresistance: Unveiling Novel Therapeutic Targets
2)Abstract (max 500 words)

Chemotherapeutic resistance significantly impedes treatment efficacy, leading to cancer recurrence, subsequent treatment failures, and ultimately, patient mortality. Some tumors may inherently resist certain drugs due to genetic factors, while others develop resistance after drug exposure. Extensive research has been conducted to identify predictive factors for resistance onset to adapt therapeutic strategies.

Recent studies reveal that cellular metabolic states influence chemotherapy response, with cancer cells reprogramming their metabolism in reaction to chemotherapeutic agents. This metabolic rewiring emerges as a crucial mechanism of acquired resistance and presents opportunities for enhancing treatment efficacy. Cancer cells adapt their metabolism to survive in harsh environments, including those induced by drug treatments. This reprogramming may involve various pathways, including glycolysis, shifts towards the pentose phosphate pathway, lipid and glutamine synthesis, and alterations in mitochondrial functions.

Our research has shown that cisplatin-resistant ovarian cells exhibit increased glucose uptake and consumption, along with enhanced expression and enzymatic activity of Glucose-6-Phosphate Dehydrogenase (G6PDH), a key enzyme in the Pentose Phosphate Pathway (PPP). Combining G6PDH inhibitors with cisplatin demonstrated a selective additive effect on cisplatin-resistant cells. To mitigate cisplatin toxicity and extend its action, we developed a lyophilized stealth liposomal formulation. The combination of G6PDH inhibitor and liposomal cisplatin showed promising cytotoxic activities in drug-resistant cells and prolonged pharmacokinetics in rats.

We have also recently demonstrated that cisplatin-resistant ovarian and osteosarcoma cells display mitochondrial dysfunction, resulting in increased mitophagy (selective mitochondrial autophagy), enabling cells to evade chemotherapy toxicity. Inhibiting autophagy through specific molecules can resensitize resistant cells to platinum-based drugs. Similar mitochondrial alterations are emerging in doxorubicin-resistant osteosarcoma cells, further supporting the role of mitochondria in chemotherapy resistance.

The primary objective of our research is to identify altered metabolic pathways in resistant cells, providing novel prognostic and predictive biomarkers for chemoresistance. Furthermore, identifying altered

metabolic targets opens up new possibilities for innovative pharmacological strategies and approaches to sensitize resistant cells to chemotherapy.